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Immunologic Basis of Clopidogrel Hypersensitivity and Diagnosis by Lymphocyte Toxicity Assay

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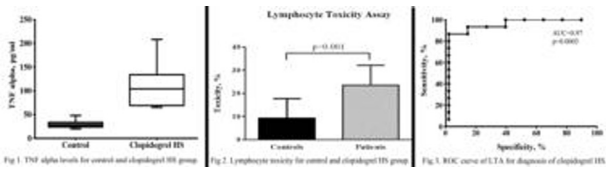
Background: Clopidogrel hypersensitivity(HS)manifesting is a recognized complication affecting ~3% of treated patients. Contrary to other drug allergy, the immunologic basis of clopidogrel HS are poorly understood. In this report, we characterize the cellular and immunologic mechanism of clopidogrel HS and describe a novel Lymphocyte Toxicity Assay (LTA) for the confirmation of diagnosis in affected individuals.
Methods: Blood and skin samples from 32 patients with a confirmed diagnosis of clopidogrel HS were analyzed for hematologic and an immunologic response during the active phase of clopidogrel HS. LTA and TNF alpha assay were performed after a minimum of 12 months post clopidogrel discontinuation.
Results: The hematological screen identified a significant increase in circulatory neutrophil and decrease in lymphocyte with no change in the eosinophil counts. The immunohistochemistry of the affected areas showed a predominance of CD4+, CD1+ with few CD8+, CD 68+ cells and absence of caspase staining. The LTA and TNF alpha values were increased for clopidogrel HS compared to control patients, figure 1 and 2. ROC curves demonstrated excellent accuracy for the diagnosis of Clopidogrel HS (figure 3) with sensitivity of 86% and specificity of 100% for LTA >16%.



Conclusions: Clopidogrel HS is mediated by cellular immunity in contrast to the humoral response seen for most other drug reactions. LTA is a novel test that offers high sensitivity and specificity for accurate diagnosis in susceptible individuals.

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Short-Duration Versus Guideline-Recommended 12-Month Dual Antiplatelet Therapy After Drug-Eluting Stents Implantation

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Background: The optimal duration of dual antiplatelet therapy (DAPT) after drug-eluting stents (DES) implantation has not been determined. Current ACCF/AHA guidelines recommend 12-month DAPT based on observational evidence suggesting an increased risk of stent thrombosis after premature DAPT cessation. We performed a meta-analysis of randomized clinical trials comparing short-term (3-6 months) DAPT with guideline-recommended DAPT (at least 12 months) in patients undergoing percutaneous coronary interventions (PCI) with DES implantation.
Methods: PubMed, EMBASE and CENTRAL were searched for published randomized trials directly comparing short-term versus ACCF/AHA guideline-recommended (at least 12 months) DAPT after PCI with DES up to March 2013. Risk ratios (RR) were used as a the metric of choice for treatment effects by using random- and fixed-effects models. I-squared index was applied to assess heterogeneity across trials. The primary safety and efficacy outcomes were any bleeding and the composite of cardiac death and myocardial infarction, respectively. The secondary efficacy outcome was definite or probable stent thrombosis. Outcomes were analyzed at maximum available follow-up.
Results: Four trials were identified: EXCELLENT (6-month vs. 12-month DAPT, N=1,443), PRODIGY (6-month vs. 24-month, N=1970), RESET (3-month vs. 12-month DAPT, N=2,117), and OPTIMIZE (3-month vs. 12-month DAPT, N=3,119) – including a total of 8,649 patients with at least 12-month follow-up. Short-term DAPT was associated with a reduced risk of any bleeding as compared to guideline-recommended DAPT (RR 0.64, 95% CI 0.46-0.89). With respect to antithrombotic efficacy, risks of cardiac death or myocardial infarction (RR 1.08, 95% CI 0.82-1.32) and definite/probable stent thrombosis (RR 1.24, 95% CI 0.76-2.02) did not differ between short-term DAPT compared with guideline-recommended DAPT. There was no statistically significant heterogeneity across trials for any of the analyzed outcomes.
Conclusions: Short-term DAPT is associated with a reduced risk of bleeding but preserves antithrombotic efficacy compared with ACCF/AHA guideline-recommended 12-month DAPT after PCI with DES implantation.

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Additive And Independent Impact Of Chronic Kidney Disease And Diabetes Mellitus On High Platelet Reactivity And Adverse Events Following PCI: Results From The ADAPT-DES Registry

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Background: Chronic kidney disease (CKD) and diabetes mellitus (DM) affect platelet function and cardiovascular risk. Despite substantial overlap, the impact of CKD and DM, in combination vs. alone, on platelet reactivity and adverse events after percutaneous coronary intervention (PCI) remains unclear.
Methods: ADAPT-DES is a prospective registry of 8,582 patients undergoing PCI with drug-eluting stents (DES). All patients underwent VerifyNow platelet function testing. We defined high platelet reactivity (HPR) after clopidogrel loading as platelet reactivity units (PRU) >208, and CKD as a creatinine clearance < 60 ml/min. We examined frequency of HPR and 2-year MACE rates in patients with CKD alone (n=881), DM alone (n=2258), both CKD and DM (n=521) and neither CKD nor DM (n=4883).
Results: HPR in patients with CKD alone, DM alone, both CKD and DM and neither CKD nor DM was 44.9%, 54.4%, 55.9% and 35.6%, respectively (p< 0.001). The 2-year composite rates of cardiac death, MI or stent thrombosis were highest in patients with both conditions, similar in those with CKD or DM alone, and lowest in the absence of either CKD or DM (Figure). After adjusting for risk factors (including HPR), hazard ratios (95% CI) for MACE were 1.56 (1.16-2.10), 1.50 (1.22-1.86) and 2.43 (1.80-3.29) in patients with CKD alone, DM alone, and both CKD and DM, compared to those without CKD or DM, respectively.
Conclusions: CKD and DM both predict HPR on clopidogrel, with additive risk. The negative prognostic impact of CKD and DM on 2-year MACE rates was greatest in patients with both conditions, independent of on-treatment platelet reactivity.